Integration of metabolism

1. **Energetic integration** (NTPs (mainly ATP) are the universal currency of energy; main electron carriers in oxidative reactions are NADH and $FADH_2$, main electron donor in reductive biosynthesis is NADPH)
2. **Metabolic reactions integration in pathways** (few key metabolites, that are key junctions/nods of metabolic pathways; biomolecules are constructed from a small set of building blocks)
3. Regulation of metabolism through enzymatic activity
4. Regulation of transport/flow of substrates

→ **3 and 4 Based first of all on protein activity regulation (→regulation of metabolites flow and enzymatic reactions velocity)**

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metabolic reactions are compartmented; biosynthesis and catabolism are usually separated in space

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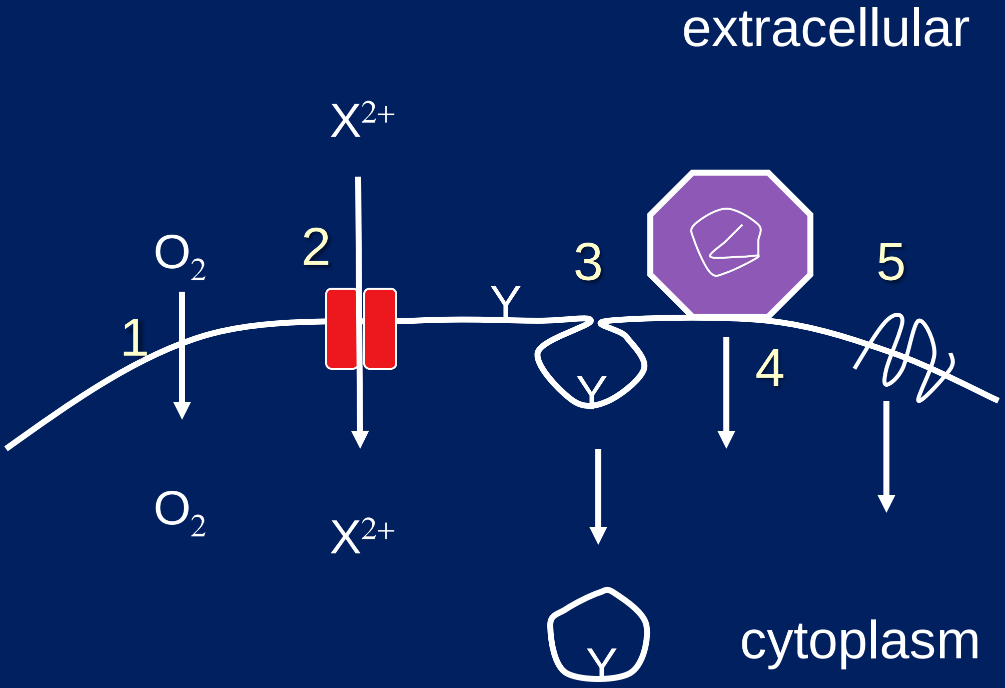
5. Compartmentation of metabolism:

metabolic reactions are compartmented; biosynthesis and catabolism are usually separated in space;

compartmentation is supported by regulated molecules' transport, sorting and assembly

Getting molecules into cells: crossing the plasma membrane

1. Diffusion across the plasma membrane /*water, gases, small molecules*
2. Protein-mediated transport /ion channels, transporters
3. Formation and internalization of membrane-limited vesicles/
   - Endocytosis
   - Pinocytosis
   - Phagocytosis
4. Membrane fusion /viruses
5. Pore formation /toxins



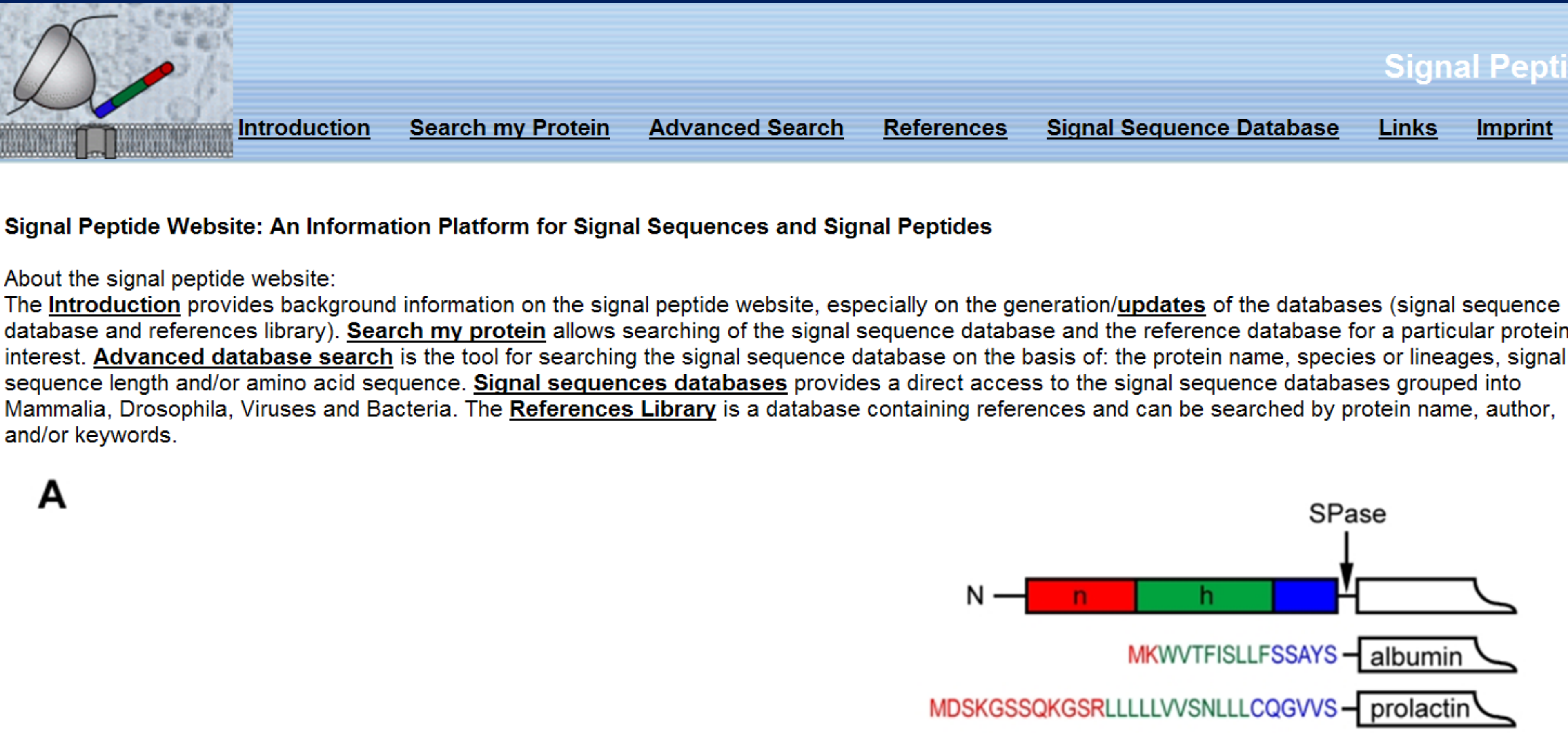
Molecules sorting

Protein direct transport and sorting

- Signal peptides/sequences
- Signal regions (part of 3D structure, modified)

Vesicles transport

Signal peptide database



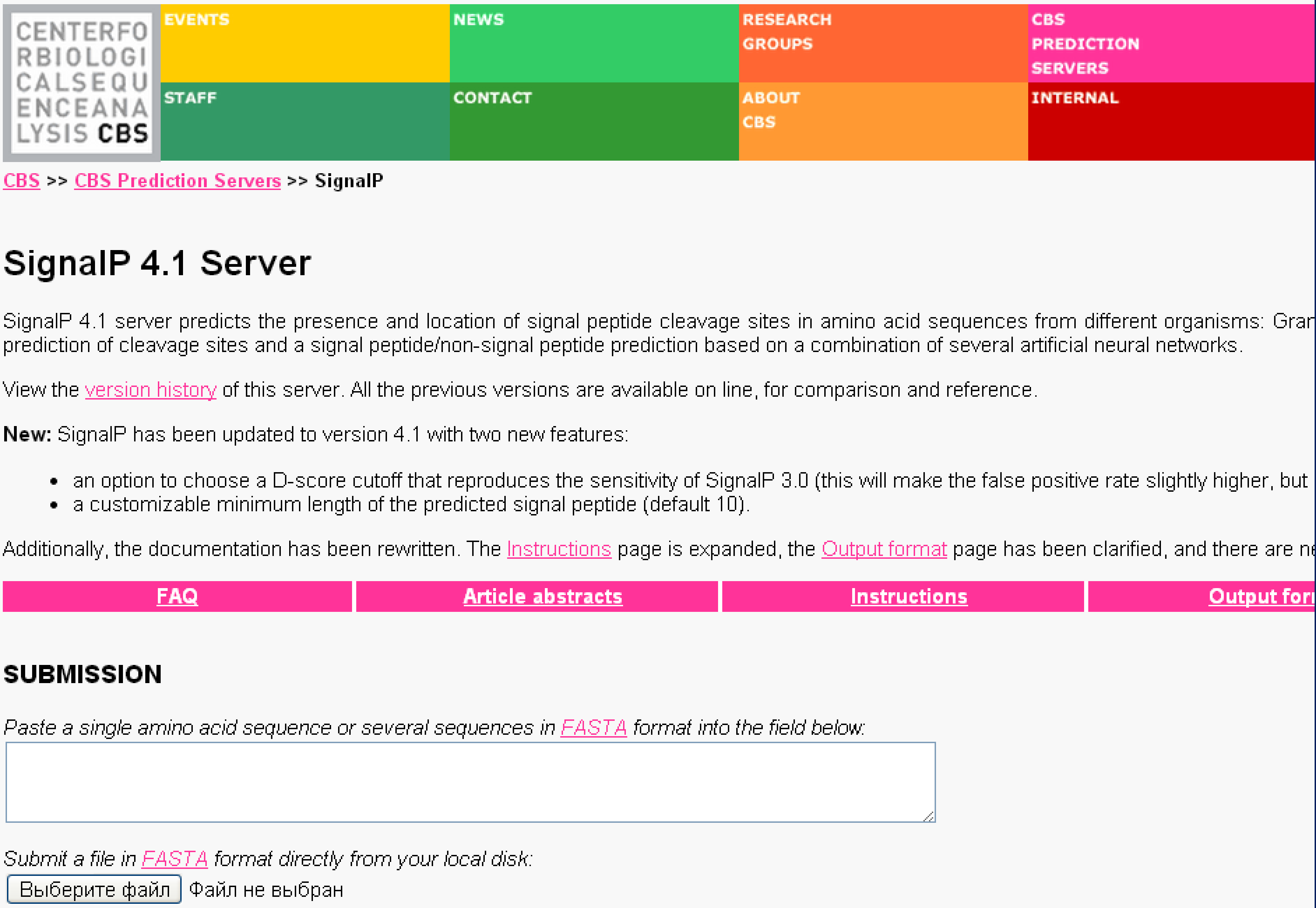
Introduction **Search my Protein** **Advanced Search** **References** **Signal Sequence Database** **Links** **Imprint**

Signal Peptide Website: An Information Platform for Signal Sequences and Signal Peptides

About the signal peptide website:
The **Introduction** provides background information on the signal peptide website, especially on the generation/**updates** of the databases (signal sequence database and references library). **Search my protein** allows searching of the signal sequence database and the reference database for a particular protein interest. **Advanced database search** is the tool for searching the signal sequence database on the basis of: the protein name, species or lineages, signal sequence length and/or amino acid sequence. **Signal sequences databases** provides a direct access to the signal sequence databases grouped into Mammalia, Drosophila, Viruses and Bacteria. The **References Library** is a database containing references and can be searched by protein name, author, and/or keywords.

http://www.signalpeptide.de/

http://www.cbs.dtu.dk/services/SignalP/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INTERNAL
CBS >> CBS Prediction Servers >> SignalP

SignalP 4.1 Server

SignalP 4.1 server predicts the presence and location of signal peptide cleavage sites in amino acid sequences from different organisms: Gran prediction of cleavage sites and a signal peptide/non-signal peptide prediction based on a combination of several artificial neural networks.

View the version history of this server. All the previous versions are available on line, for comparison and reference.

New: SignalP has been updated to version 4.1 with two new features:

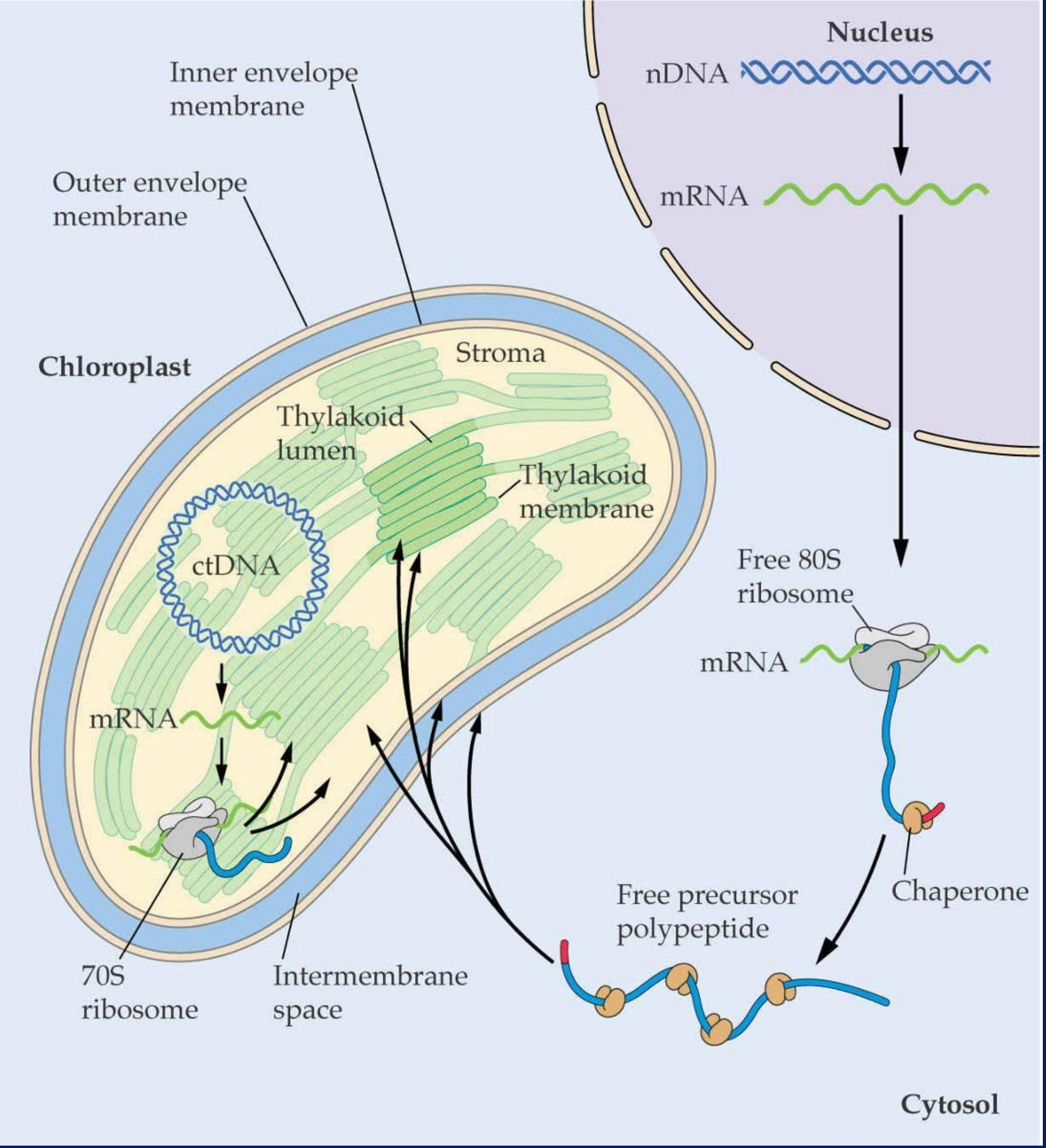
- an option to choose a D-score cutoff that reproduces the sensitivity of SignalP 3.0 (this will make the false positive rate slightly higher, but
- a customizable minimum length of the predicted signal peptide (default 10).

Additionally, the documentation has been rewritten. The Instructions page is expanded, the Output format page has been clarified, and there are ne

SUBMISSION

Paste a single amino acid sequence or several sequences in FASTA format into the field below:

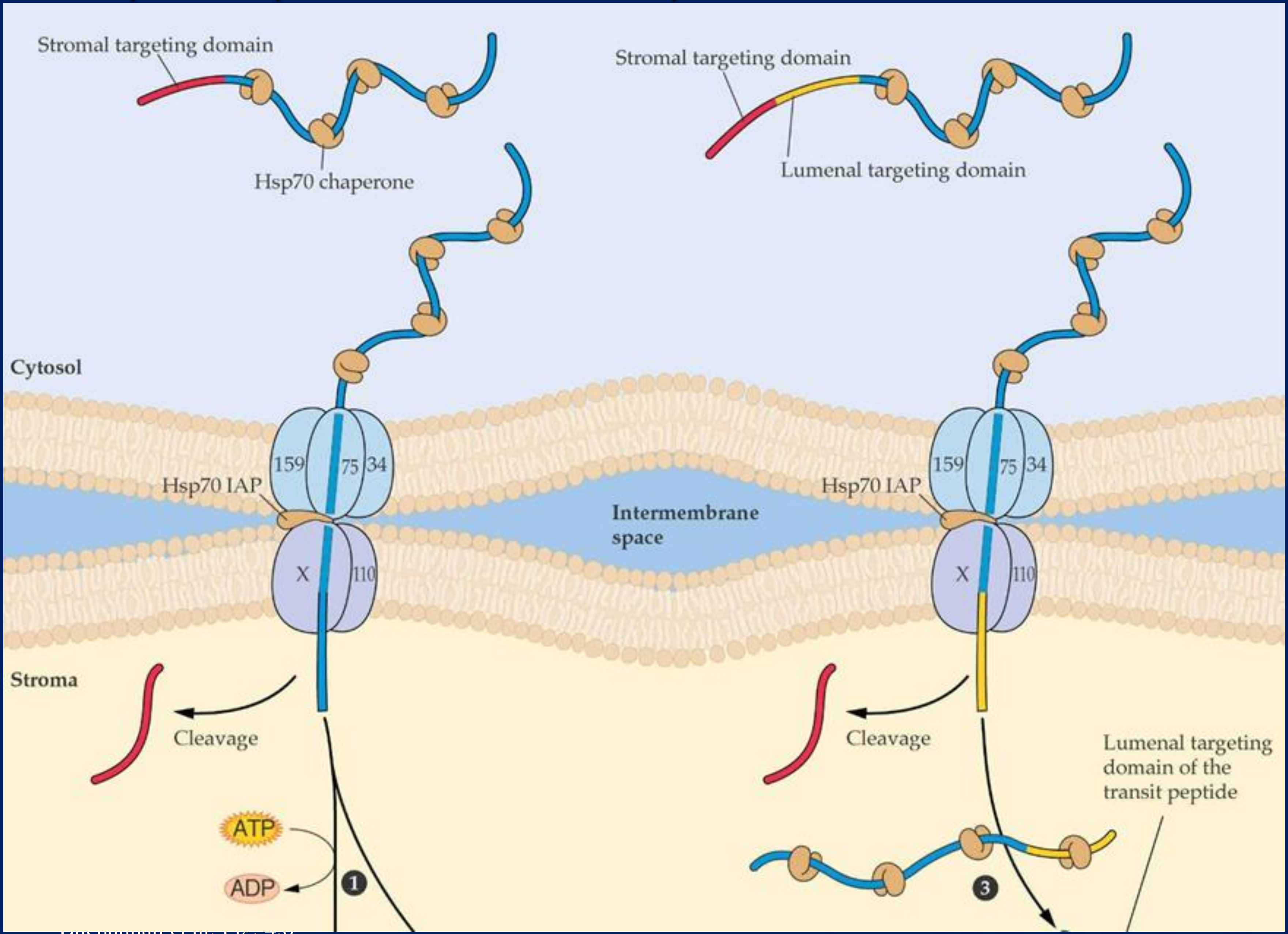
Submit a file in FASTA format directly from your local disk:



DNA for chloroplast proteins can be in the nucleus or chloroplast genome

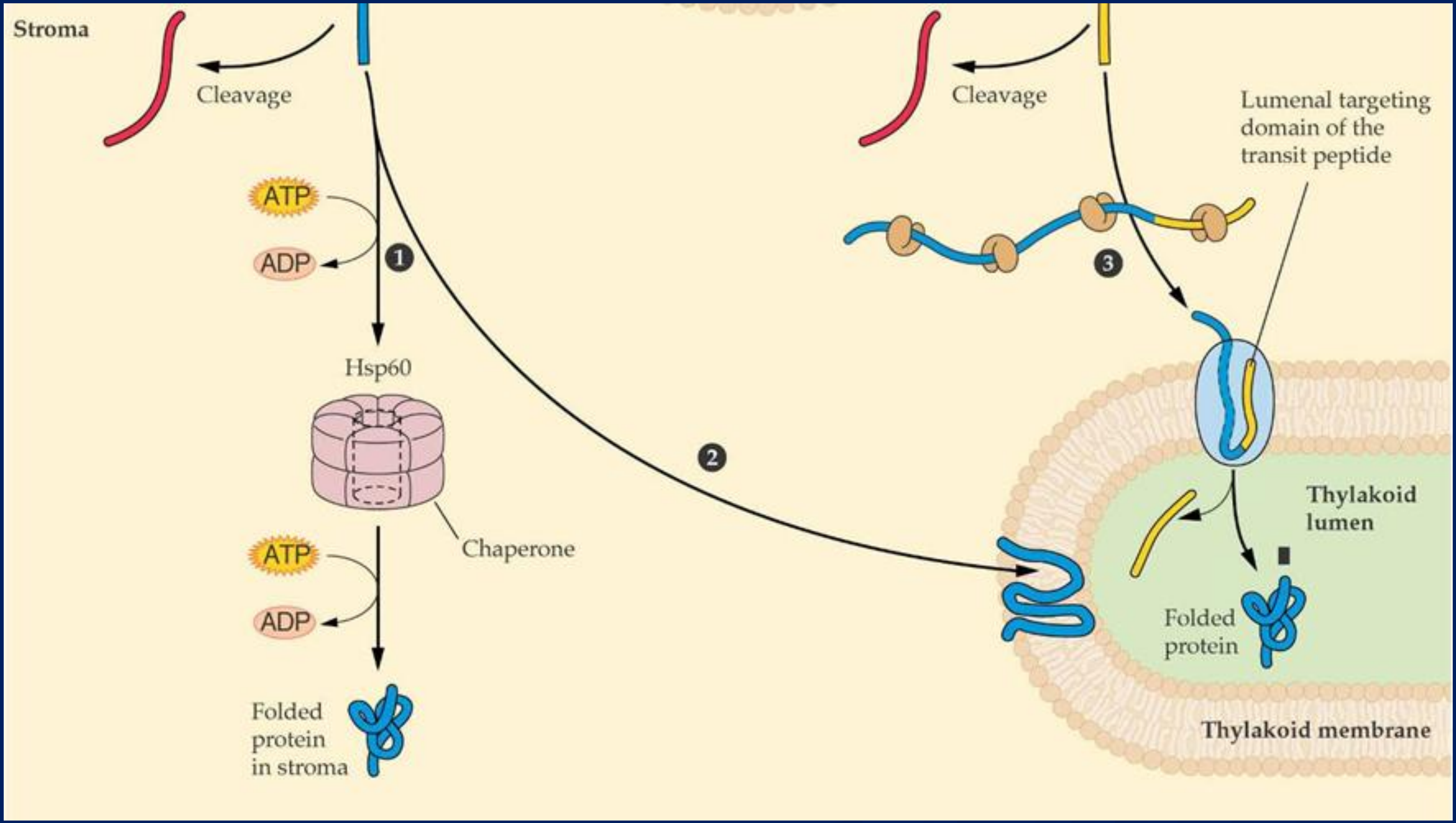
Buchannan et al. Fig. 4.4

Import of proteins into chloroplasts

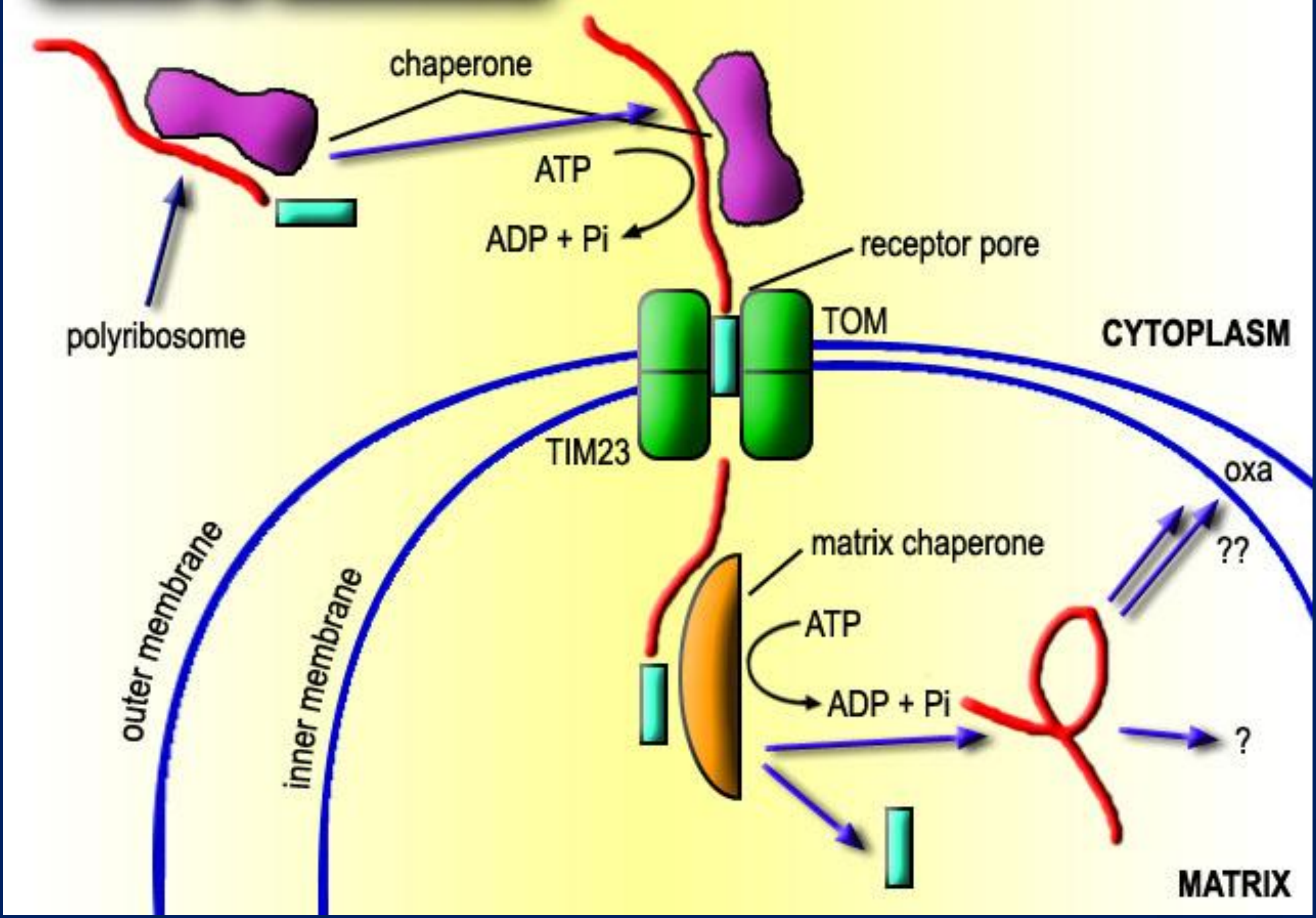


Buchanan et al. Fig. 4.6

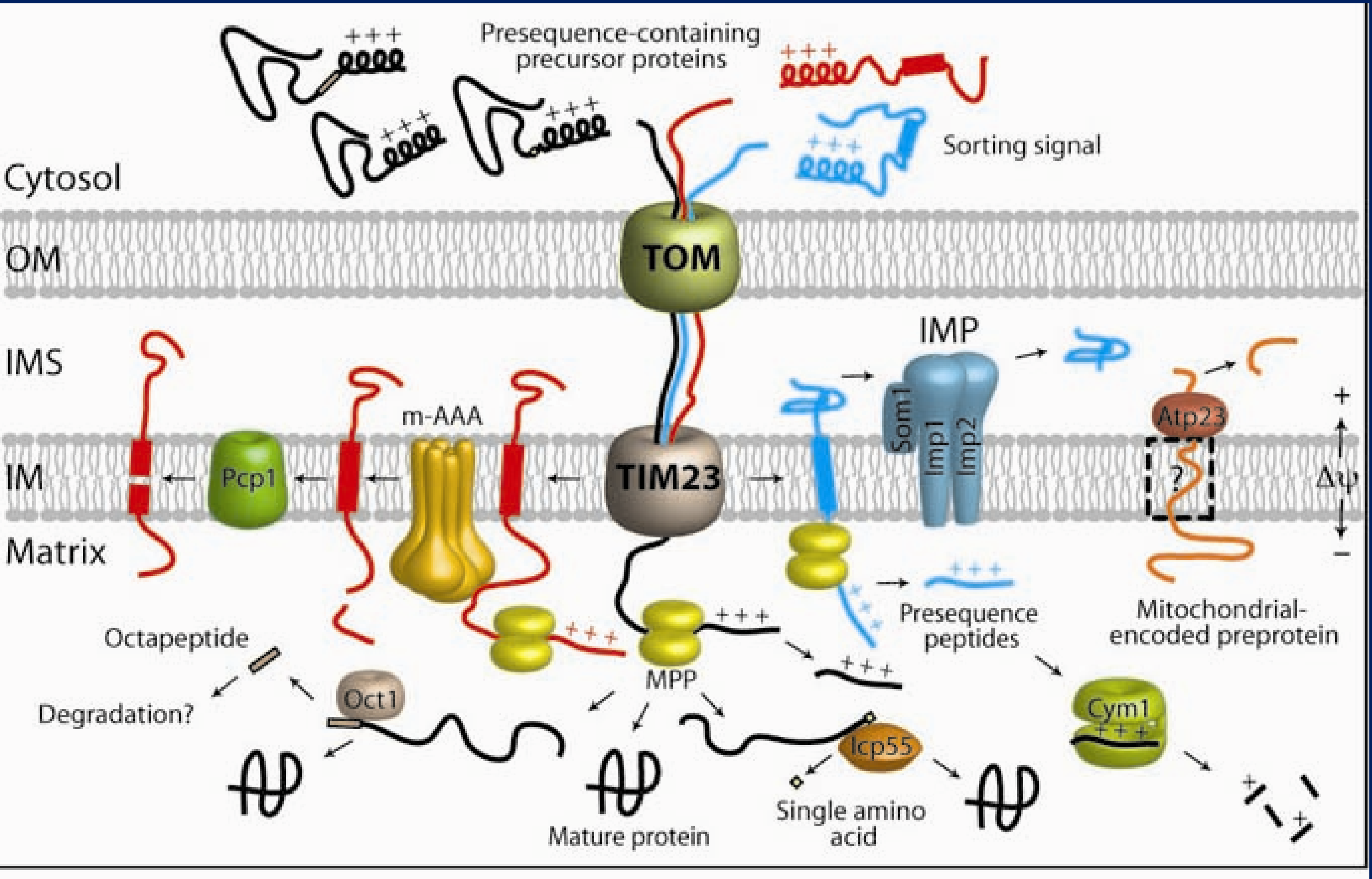
Import of proteins into chloroplasts



Growth of Mitochondria

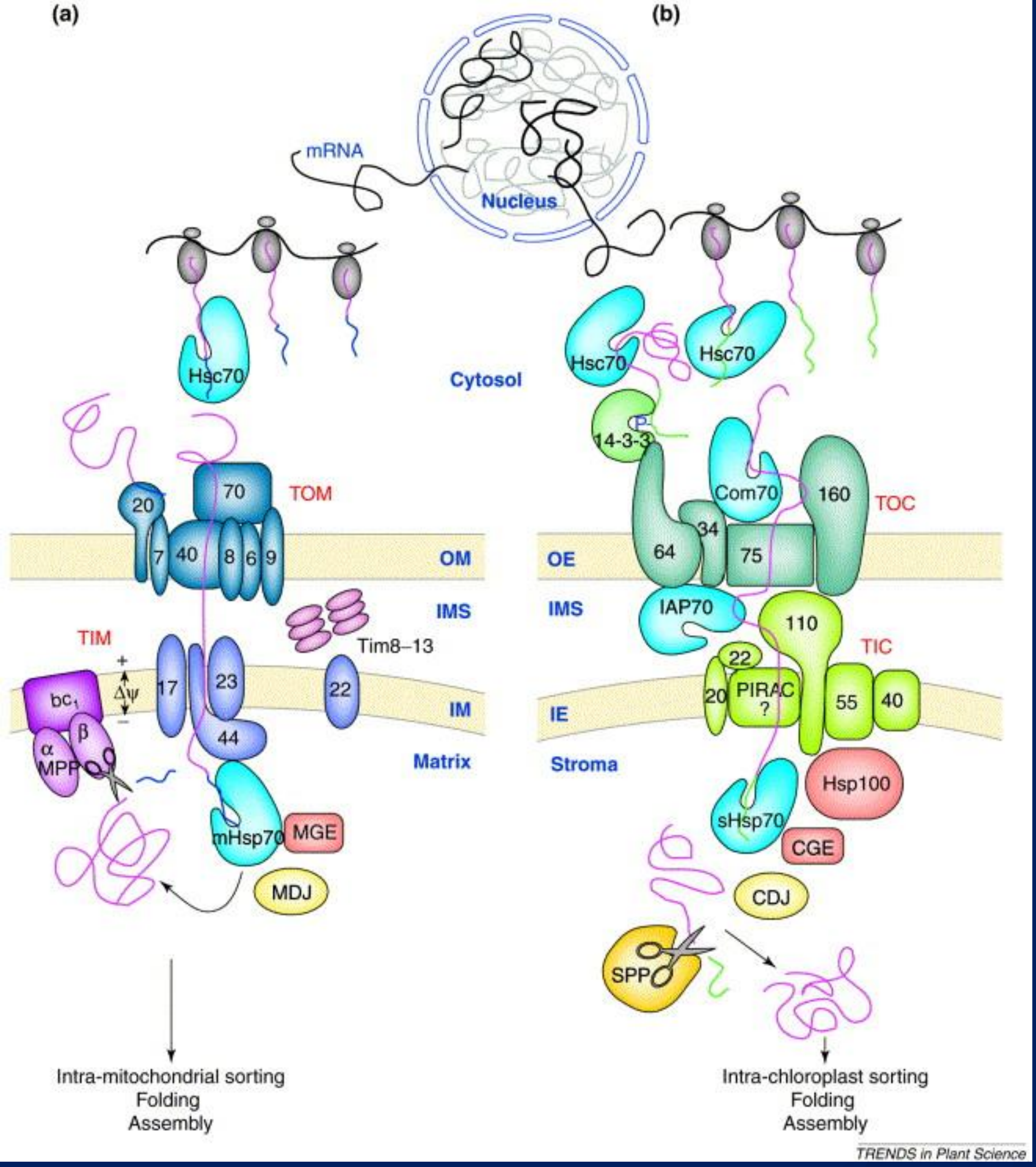


Processing of mitochondrial presequences



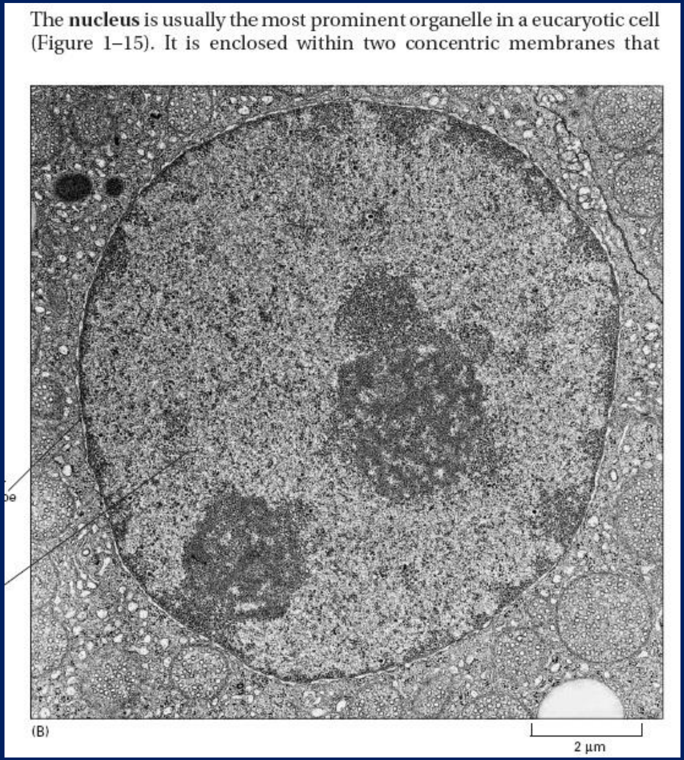
http://www.bioss.uni-freiburg.de/cms/2126.html

Interaction of plant mitochondrial and chloroplast signal peptides with the Hsp70 molecular chaperone

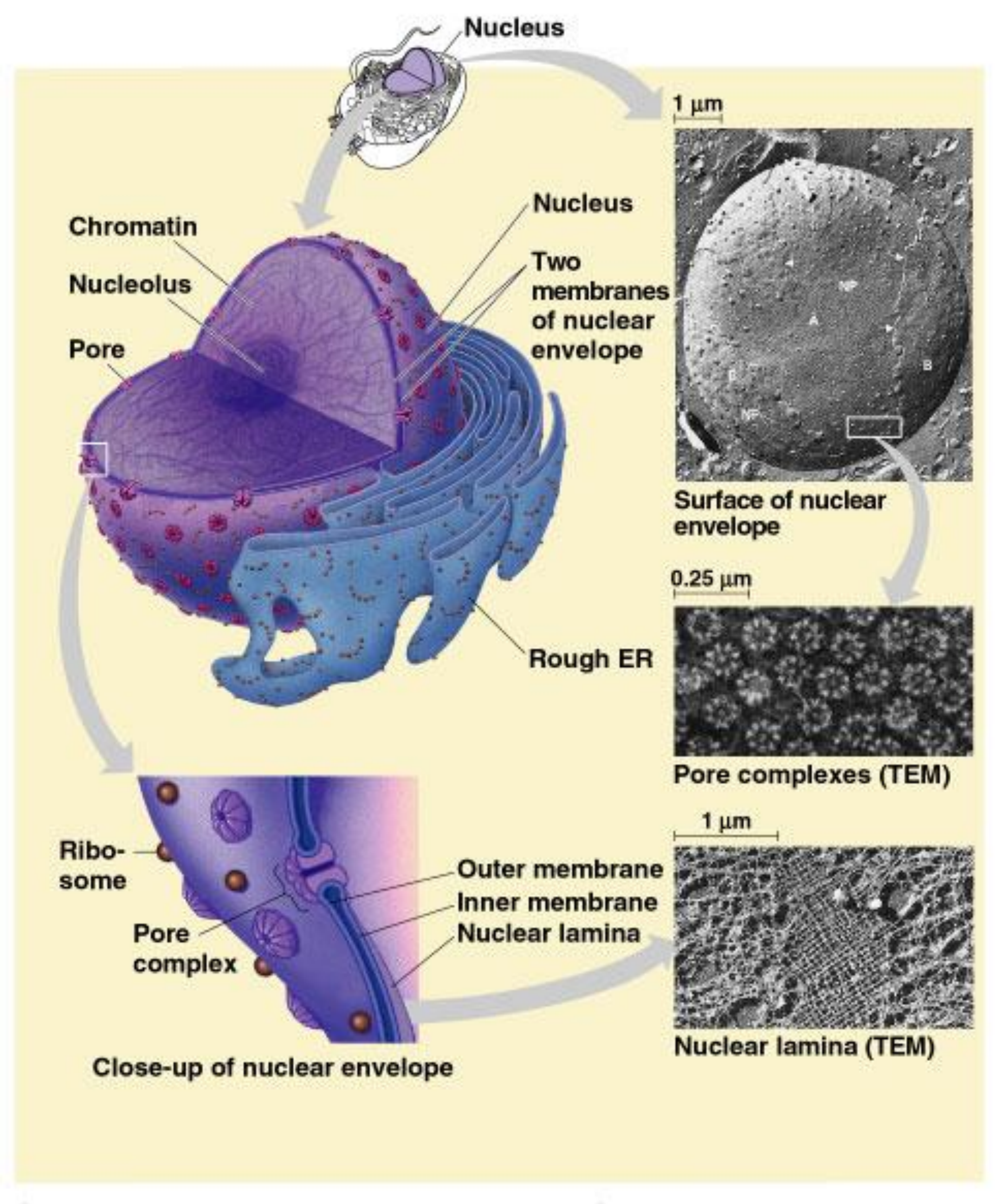


TRENDS in Plant Science

Роль сигнальных участков белков: транспорт через ядерную пору и в пероксисомы



The **nucleus** is usually the most prominent organelle in a eucaryotic cell (Figure 1–15). It is enclosed within two concentric membranes that



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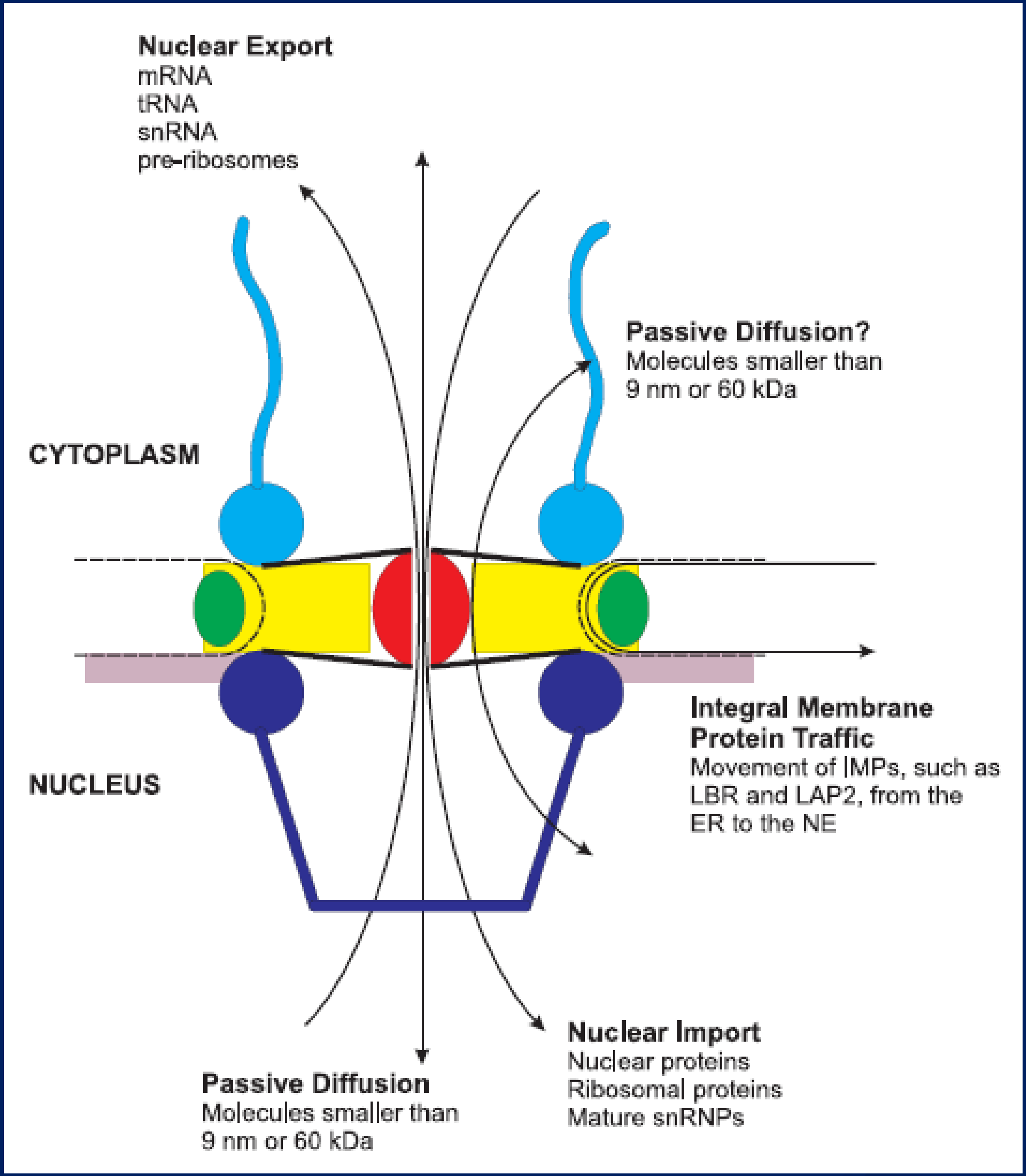
Транспорт через ядерную пору



Nuclear Export
mRNA
tRNA
snRNA
pre-ribosomes

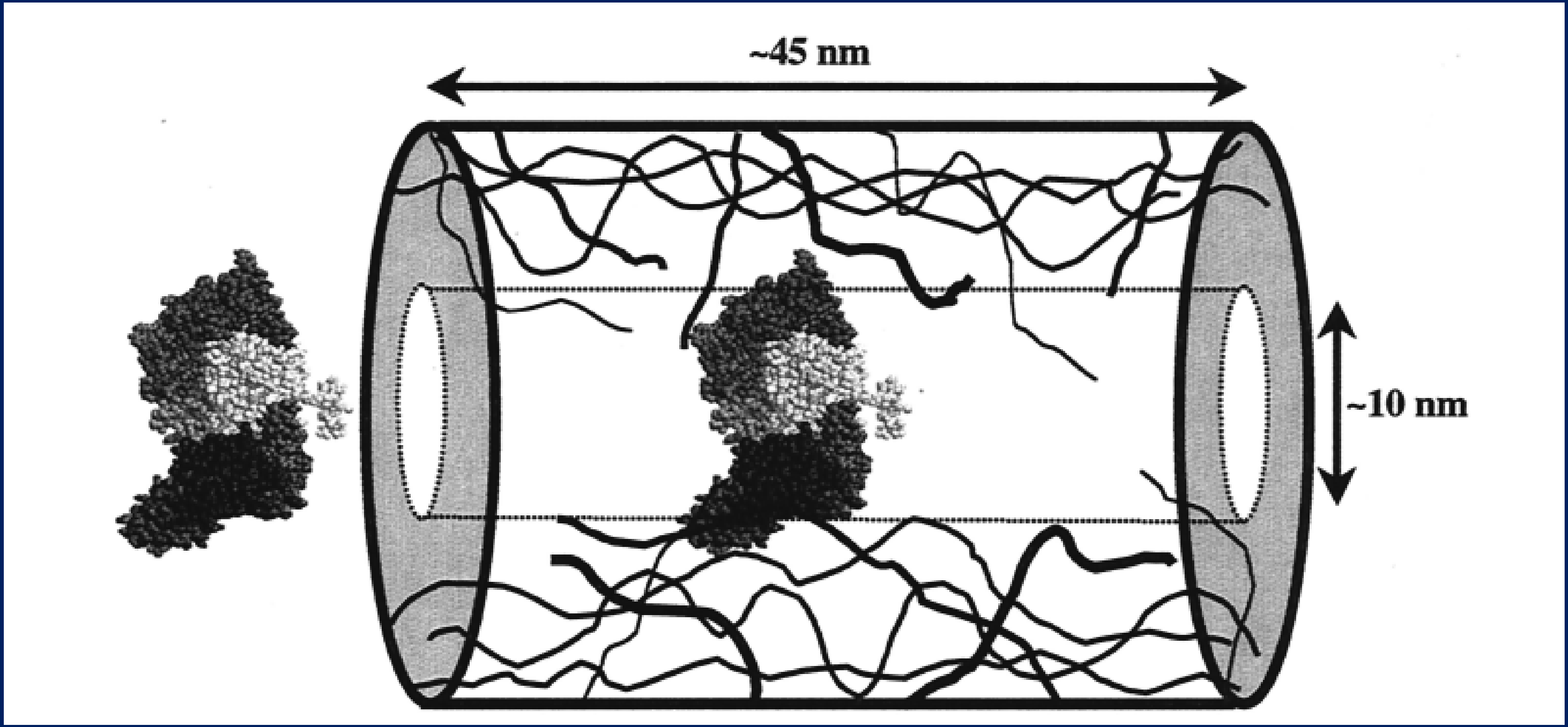
Passive Diffusion?
Molecules smaller than
9 nm or 60 kDa

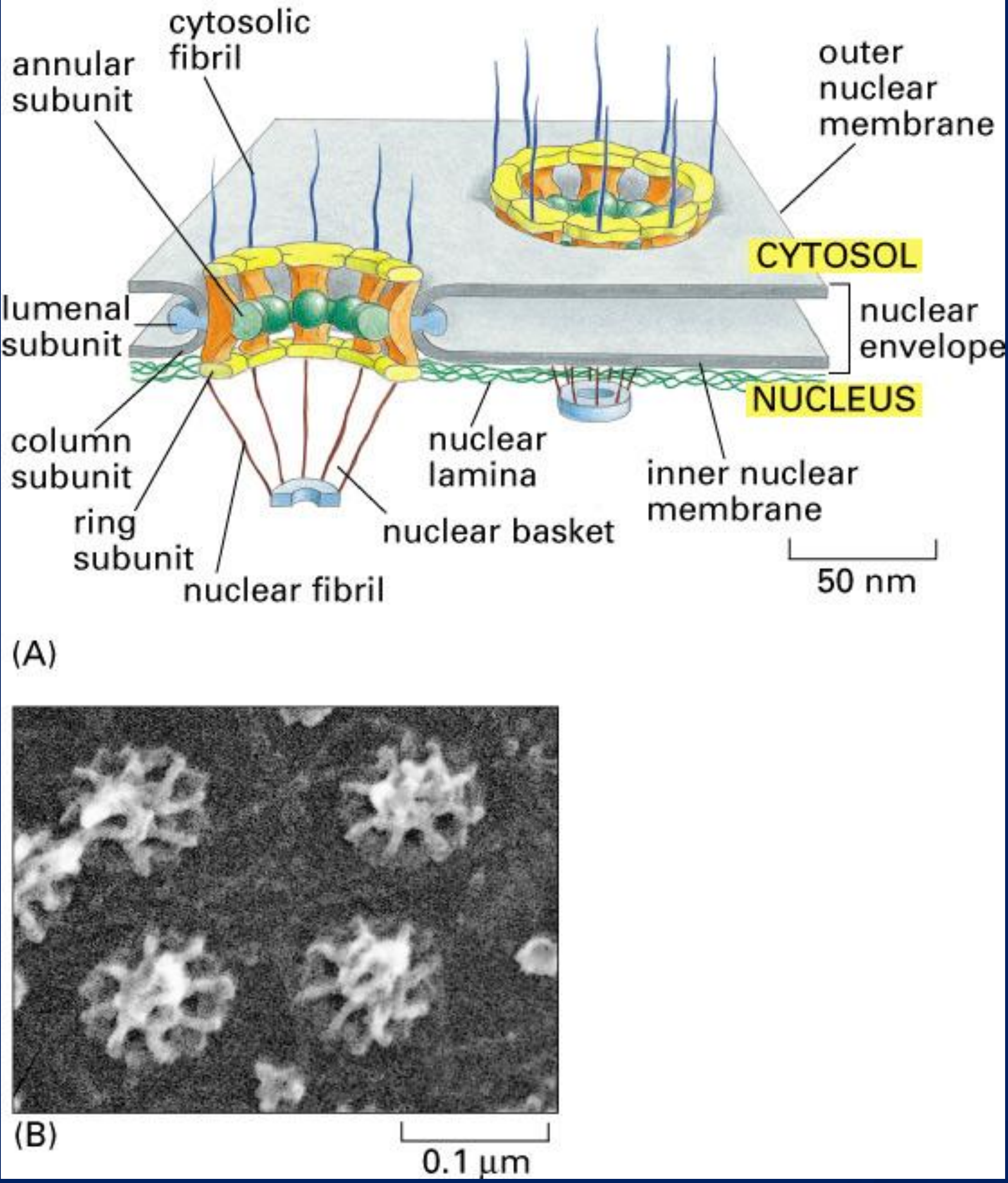
Integral Membrane Protein Traffic
Movement of IMPs, such as LBR and LAP2, from the ER to the NE

Nuclear Import
Nuclear proteins
Ribosomal proteins
Mature snRNPs

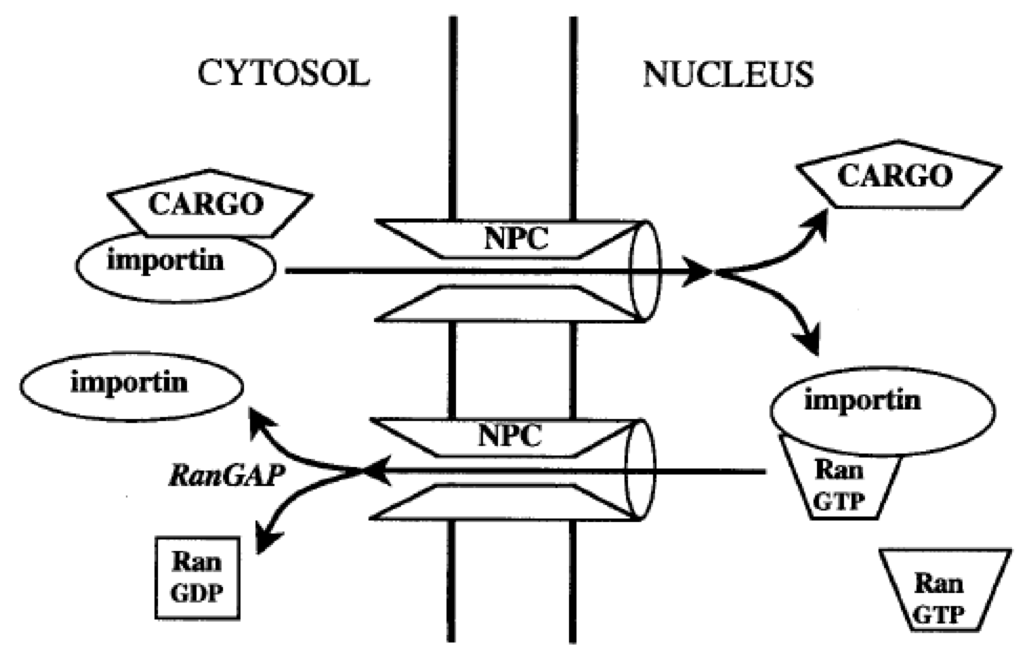
Passive Diffusion
Molecules smaller than
9 nm or 60 kDa

Transport into and out of the Nucleus





The nuclear pore complex is an aqueous channel that allows diffusion of small molecules and proteins up to 60kD. Hence, transport of such molecules is passive.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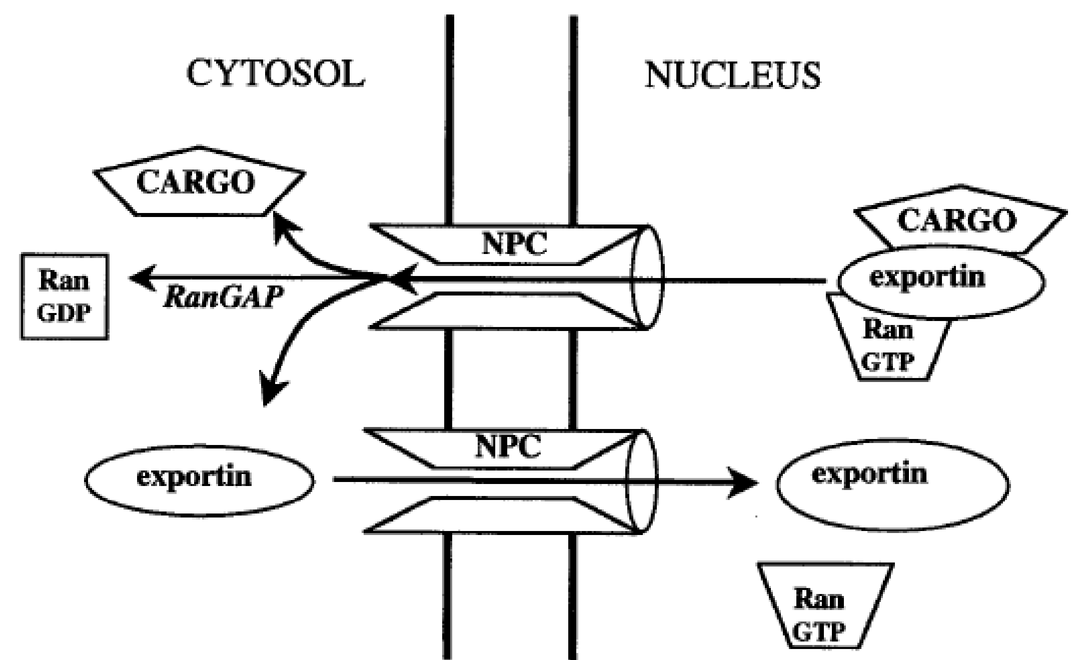
CYTOSOL
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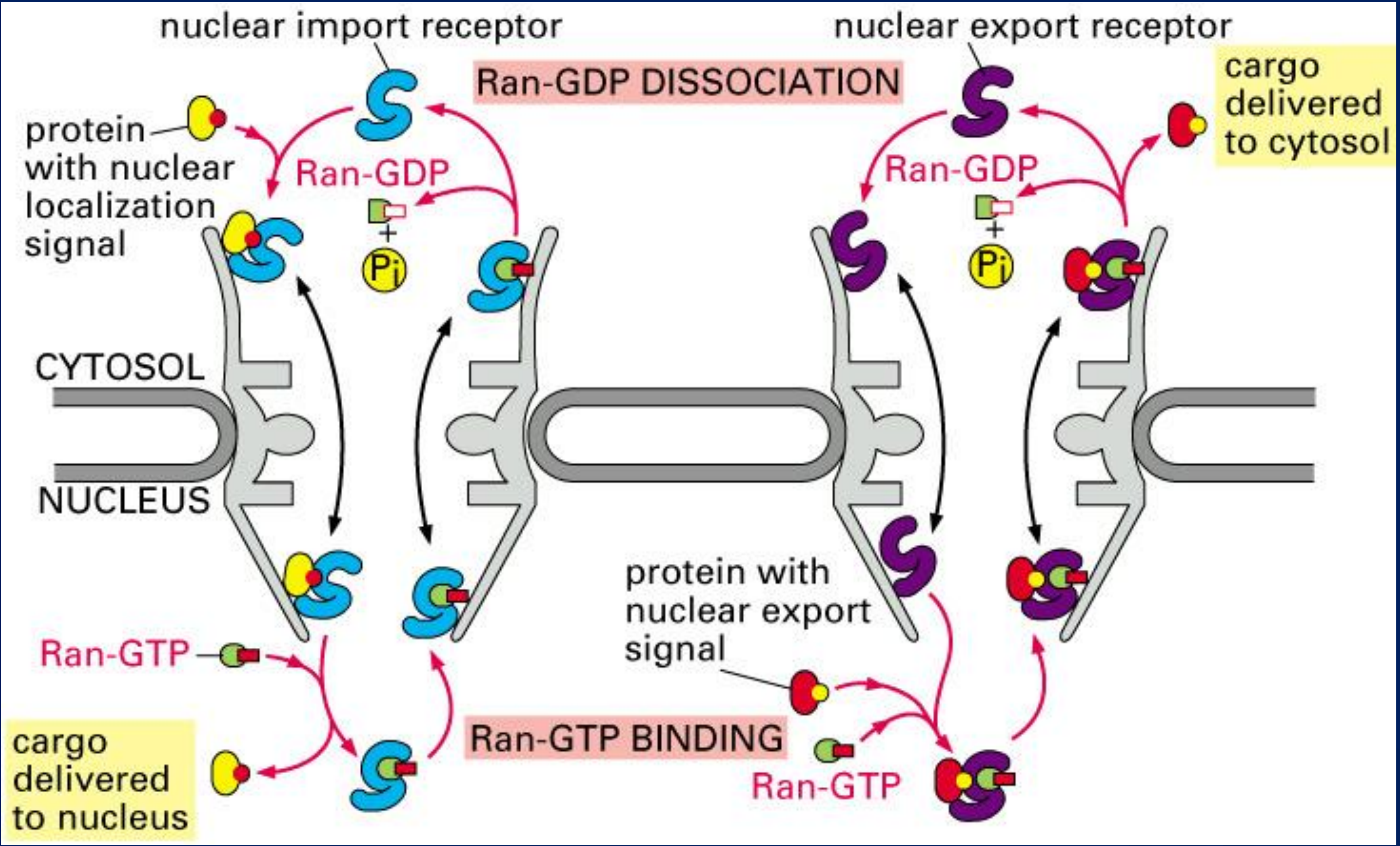


NLS=nuclear localization signal
NES=nuclear export signal

Цикл обмена ГТФаз Ran

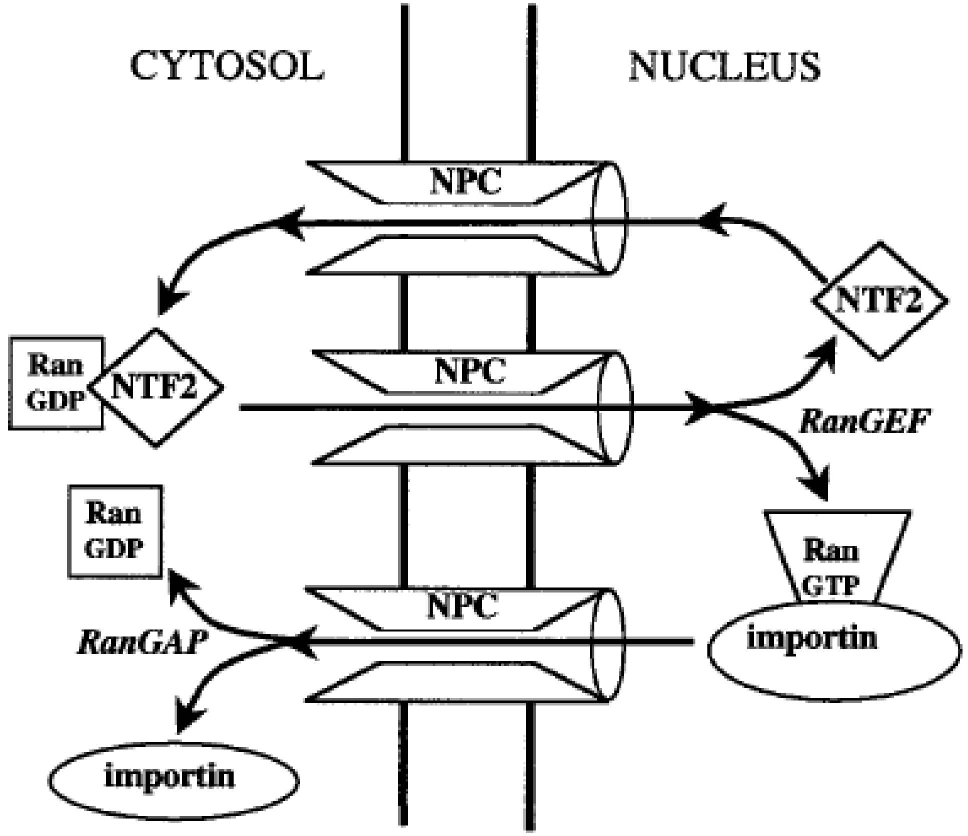
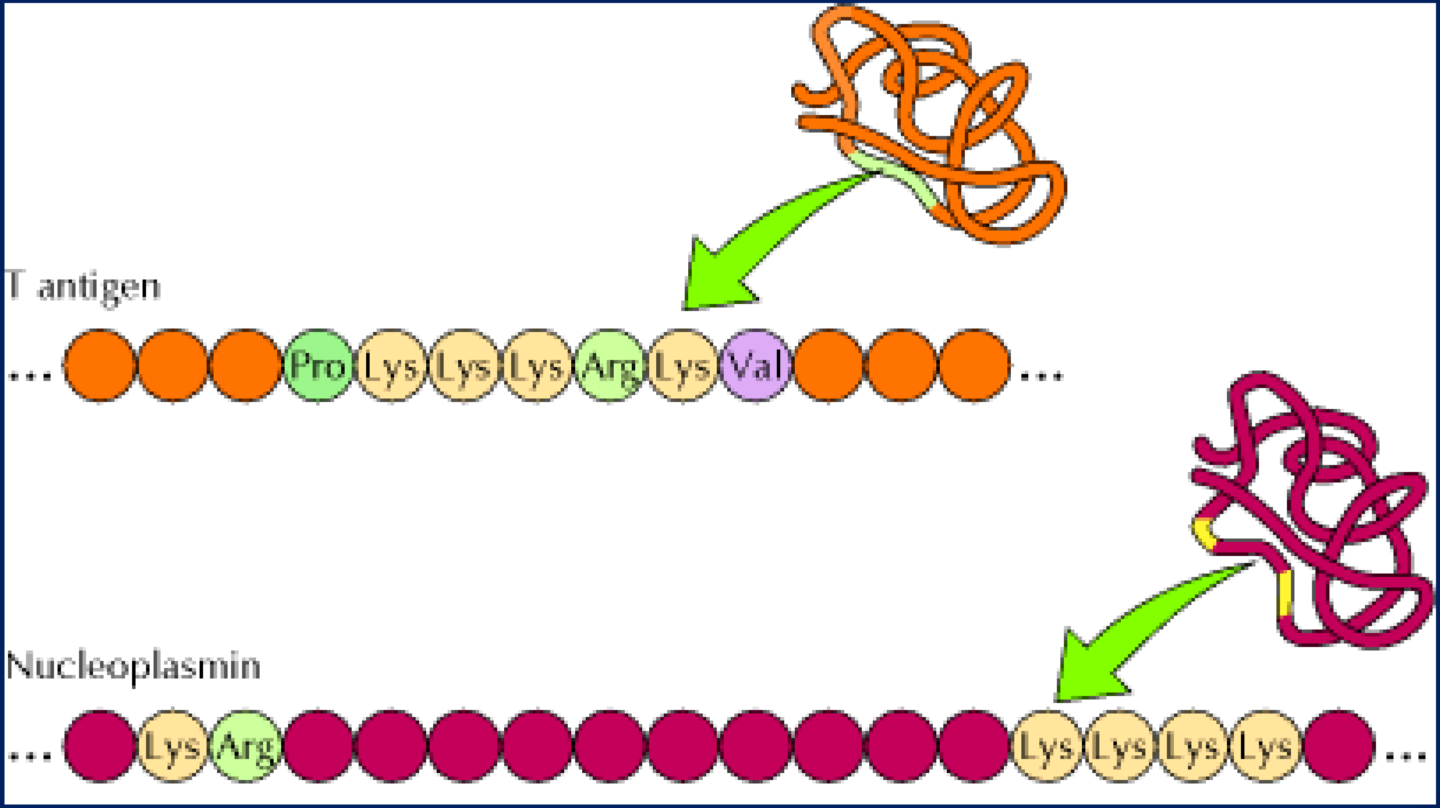
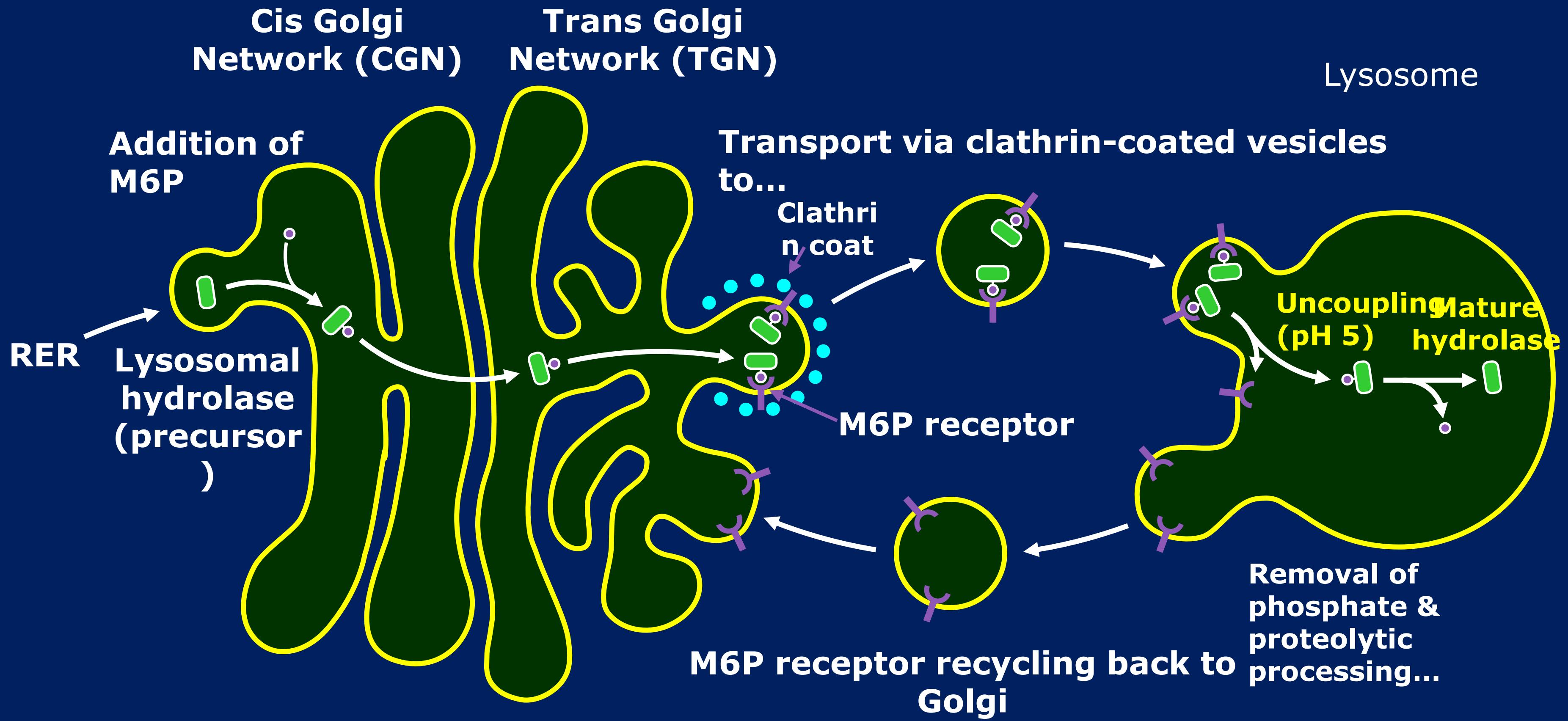


FIG. 8. Mechanism of Ran import. The carrier NTF2 binds specifically to RanGDP, present in the cytoplasm. In the nucleus, RanGEF catalyzes the exchange of GDP for GTP on Ran, which releases the NTF2. NTF2 then returns empty to the cytoplasm to pick up another molecule of RanGDP. The RanGTP associates with carriers (importins or exportins) which move to the cytosol, where the GTP is hydrolyzed, releasing RanGDP.

NLSs are short sequences rich in positively charge amino acids (K & R).



Mannose-6-P targets proteins from Golgi to lysosome



Cis Golgi Network (CGN)

Trans Golgi Network (TGN)

Lysosome

Addition of M6P

Transport via clathrin-coated vesicles to…

Clathrin coat

RER

Lysosomal hydrolase (precursor)

Uncoupling (pH 5)

Mature hydrolase

M6P receptor

Removal of phosphate & proteolytic processing…

M6P receptor recycling back to Golgi

Addition of M6P to lysosomal enzymes in cis-Golgi

M6P receptor in TGN directs transport of enzymes to lysosome via clathrin-coated vesicles

Mannose-6-Phosphate

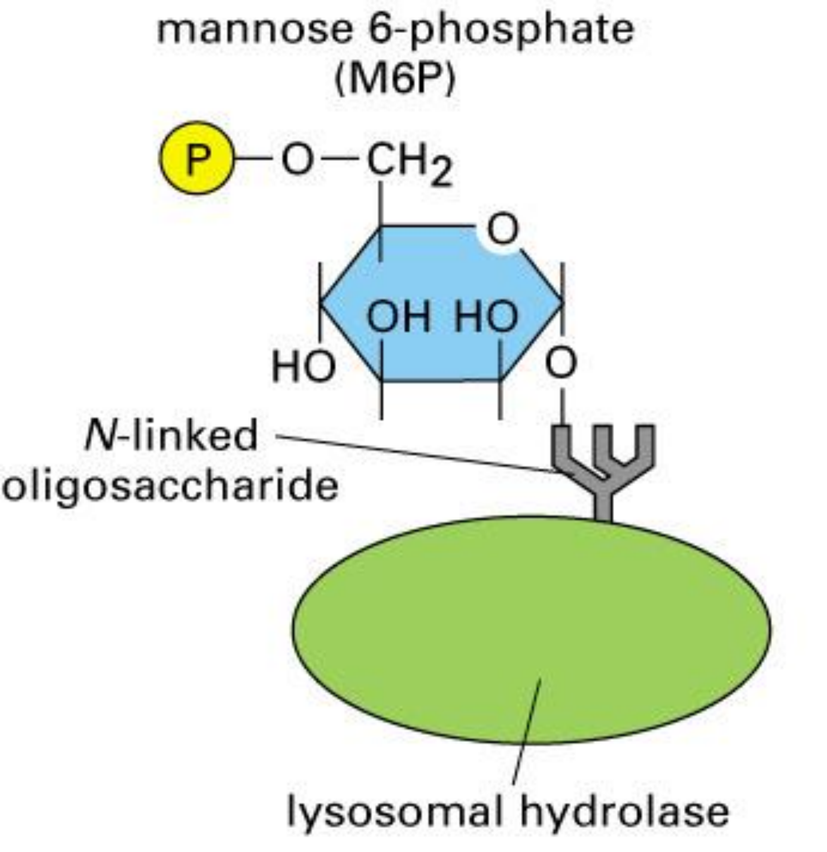
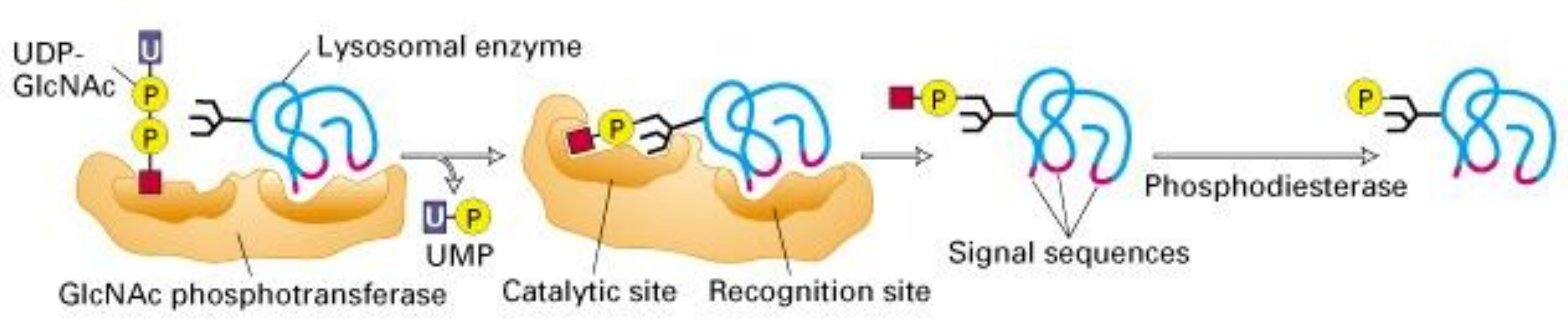


Figure 13–36. Molecular Biology of the Cell, 4th Edition.

M6P modification is the key to sorting certain lysosomal enzymes during biosynthesis.

Mechanism of Mannose 6-phosphate addition



GlcNAc phosphotransferase transfers N-acetylglucosamine phosphate to mannose on lysoson
Enzyme (e.g. Cathepsin D).

A phosphodiesterase removes the GlcNAc, leaving the phosphorylated mannose.

Phosphorylated mannose is a signal recognized by the Mannose-6-phosphate receptor.

The mannose 6-phosphate (M6P) pathway

Sorting of lumenal proteins can occur by binding transmembrane receptors.

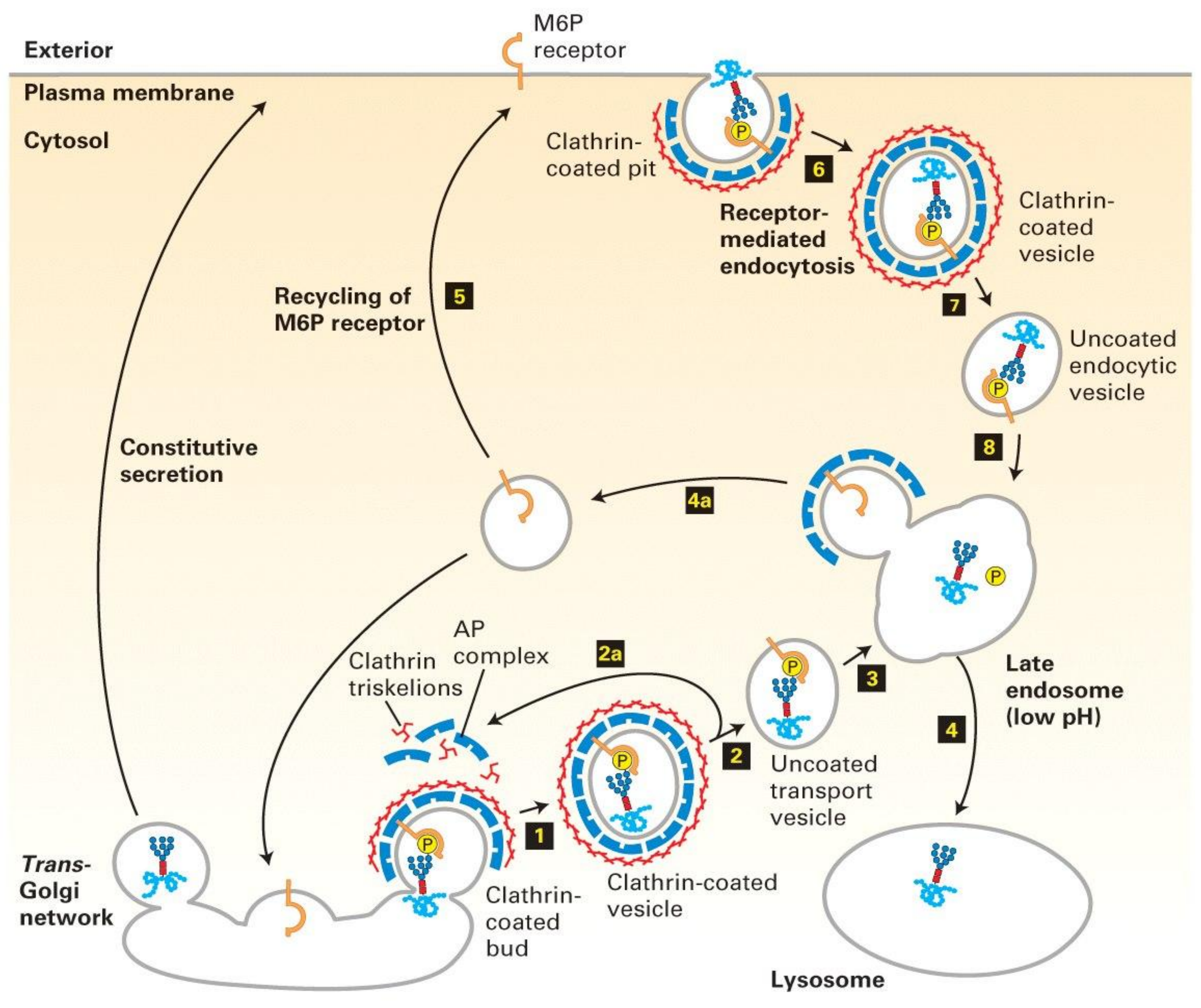
Lysosomal enzymes modified with M6P are bound by the lumenal domain of MP6R.

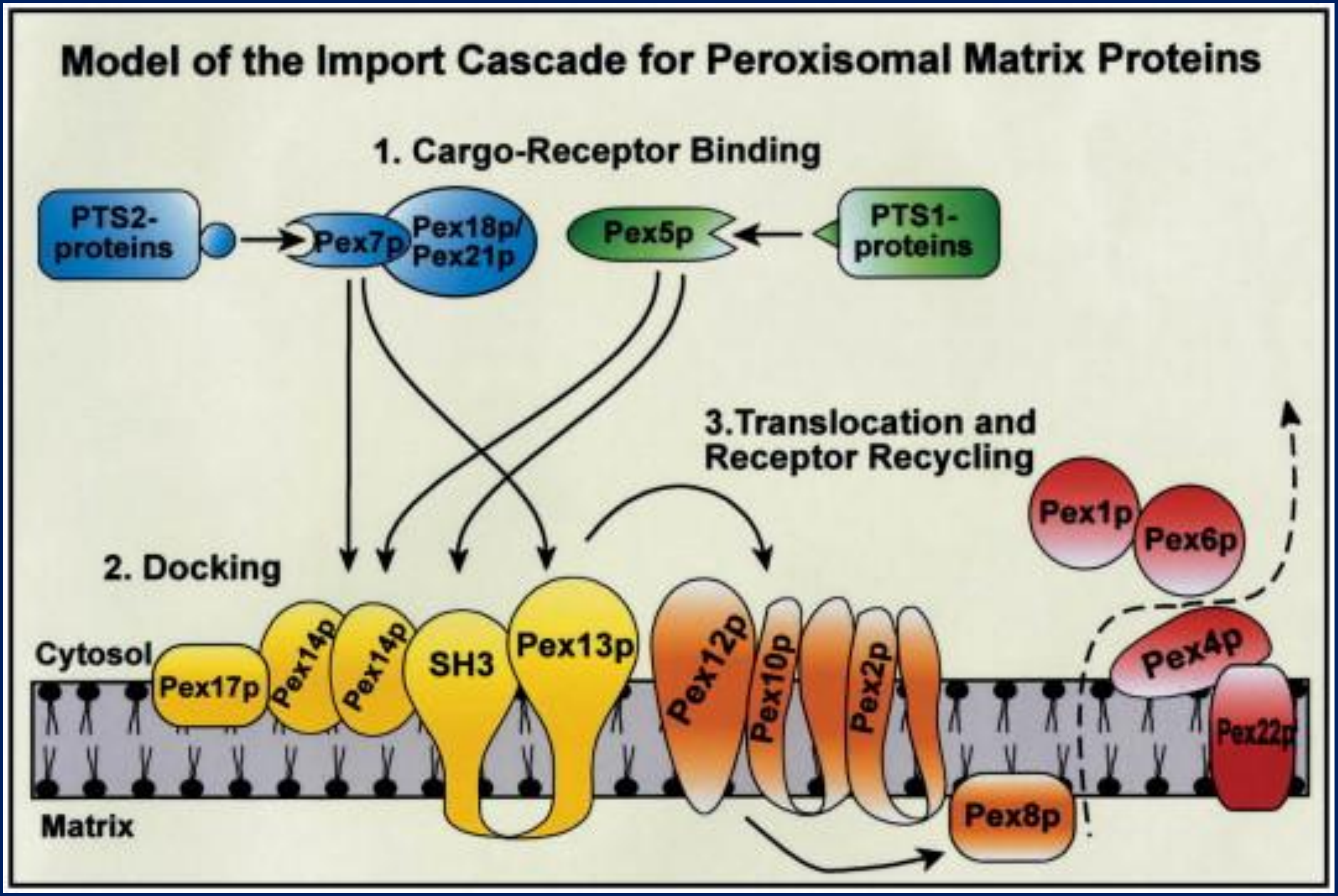
MP6R-lysosomal enzyme complexes are recruited into clathrin/AP1 coated pits.

Vesicles deliver the MP6R-lysosomal enzyme complexes to the late endosome.

MP6R recycles to the golgi.

Lysosomal enzymes are delivered to lysosomes.





Model of the Import Cascade for Peroxisomal Matrix Proteins

Biogenesis and function of peroxisomes

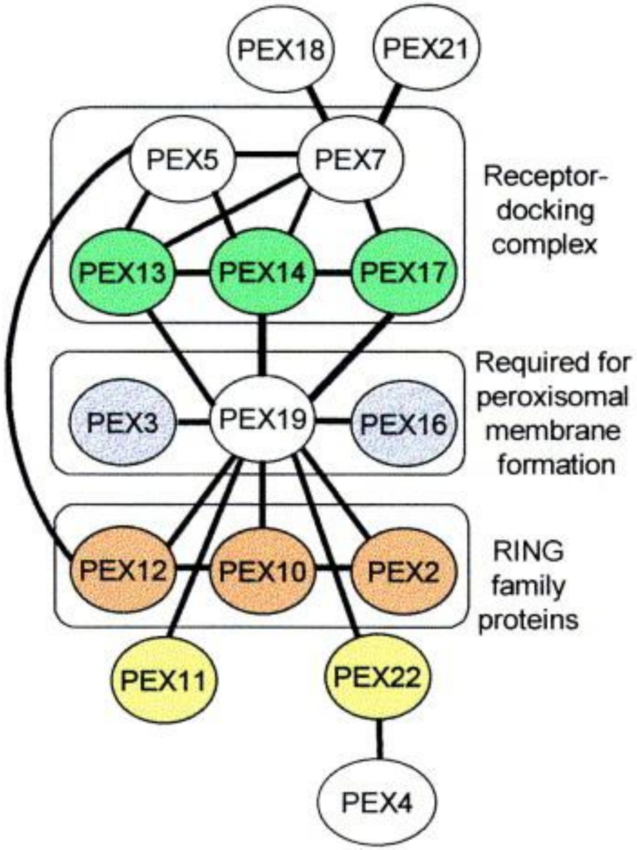


Fig. 1

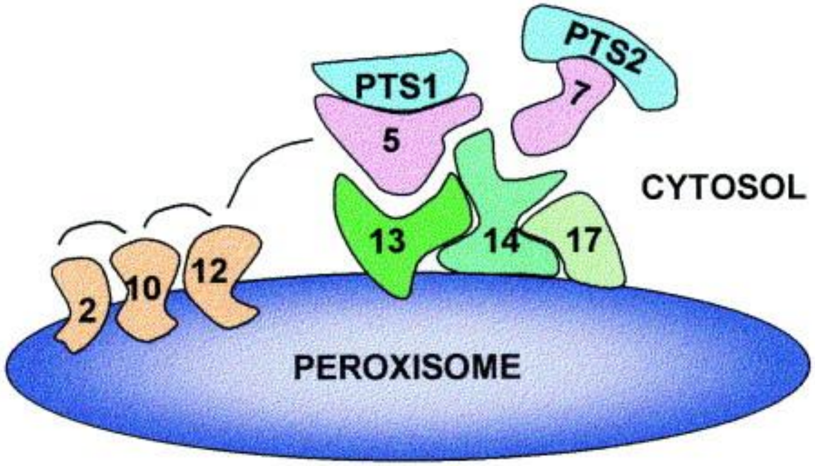


Fig. 2

Protein targeting, revised

Secretion/membrane proteins